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10/524,650	02/17/2005	Magnus Wilhelm Walter	X-15172	8466
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ELI LILLY & COMPANY PATENT DIVISION P.O. BOX 6288 INDIANAPOLIS, IN 46206-6288			EXAMINER ANDERSON, REBECCA L	
			ART UNIT	PAPER NUMBER
			1626	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary

Application No.

10/524,650

Applicant(s)

WALTER ET AL.

Examiner

Rebecca L. Anderson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9,14,15,17 and 18 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1,2,8,9,14,15,17 and 18 is/are rejected.
- 7) ☒ Claim(s) 1,3-7,14,15,17 and 18 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. <u>20070822</u> . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>2/17/05</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Claims 1-9, 14, 15, 17 and 18 are currently pending in the instant application.

Claims 1, 3-7, 14, 15, 17 and 18 are objected and claims 1, 2, 8, 9, 14, 15, 17 and 18 are rejected.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-9, 14, 15, 17 and 18 drawn to products, processes and methods wherein A is O.

Group II, claim(s) 1-9, 14, 15, 17 and 18 drawn to products, processes and methods wherein A is S.

The claims herein lack unity of invention under PCT rule 13.1 and 13.2 since, under 37 CFR 1.475(a)

Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features...those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Groups I-II lack unity of invention since under 37 CFR 1.475: the technical feature corresponding to the claims is the formula (I). This technical feature is not a special technical feature because it fails to define a contribution over the prior art as can be seen by GB 01412546, which discloses compounds of the formula (I), such as in example 1, 2-(2-n-propoxyphenylthio)-methylmorpholine hydrochloride. Therefore

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claims 1-9, 14, 15, 17 and 18 are not so linked as to form a single general inventive concept and there is a lack of unity of invention because they lack a special technical feature as the technical feature present fails to define a contribution over the prior art. Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper.

Therefore, since the claims do not relate to a single general inventive concept under PCT Rule 13.1 and lack the same or corresponding special technical feature, the claims lack unity of invention and should be limited to only a product or a method of use.

Furthermore, in regards to groups I-II even if unity of invention under 37 CFR 1.475(a) is not considered lacking, which it is, under 37 CFR 1.475(b) a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations:

- (1) A product and a process specially adapted for the manufacture of said product; or
- (2) A product and a process of use of said product; or
- (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
- (4) A process and an apparatus or means specifically designed for carrying out the said process; or
- (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

And, according to 37 CFR 1.475(c)

if an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b), unity of invention might not be present.

Therefore, since the claims are drawn to more than a product, a method and a process, and according to 37 CFR 1.475 (e)

the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

The claims, therefore, lack unity of invention.

During a telephone conversation with Thomas Jackson on 21 August 2007 a provisional election was made to prosecute the invention of Group II claims 1-9, 14, 15, 17 and 18 wherein A is S. Affirmation of this election must be made by applicant in replying to this Office action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

Claims 3-7 are objected to as being dependent upon a rejected base claim, but would appear allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 1, 8, 9, 14, 15, 17 and 18 are objected to as containing non-elected subject matter. Claims 1, 8, 9, 14, 15, 17 and 18 presented drawn solely to the elected invention wherein A is S would overcome this objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 14, 15 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the curative treatment of ADHD and the method of selectively inhibiting the reuptake of norepinephrine for the curative treatment of ADHD does not reasonably provide enablement for the prophylactic treatment or ADHD or the curative or prophylactic treatment of any disorder associated with norepinephrine dysfunction or the selectively inhibiting the reuptake of norepinephrine for the treatment, curative or prophylactic, of any other disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In In re Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case,

The nature of the invention

Claim 14 is drawn to a method of inhibiting the reuptake of norepinephrine, which, as stated in the specification, is useful for the treatment, curative and prophylactic of diseases such as ADHD, Alzheimer's disease, urinary incontinence, pain etc. Claims 15 and 17 are drawn to the treatment, curative and prophylactic of diseases such as Alzheimer's disease, urinary incontinence, ADHD, pain, etc.

It is noted that the claims 14 and 15 as written include diseases that are known to exist and those that may be discovered in the future, for which is there is no enablement.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat, curative or prophylactic, which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant

case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic and preventive effects of diseases applicant considers associated with norepinephrine dysfunction, whether or not the disease is effected by the reuptake of norepinephrine would make a difference along with whether any of the compounds can inhibit this.

For example, for the treatment of pain, acute pain and chronic pain differ in etiology, mechanisms, pathophysiology, symptomatology, diagnosis, therapy and physiological responses.

It is the state of the art that there is no known cure or prevention for Alzheimer's disease and that there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer's disease, Aricept, Exelon, Reminyl and Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease. (URL:<http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html>).

Furthermore, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can

alter the progress of the disease" (pg. 1994).

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment the inhibition of the reuptake of norepinephrine, one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role of the inhibition of the reuptake of norepinephrine.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the listing of diseases applicant considers as treatable on pages 10-11 and in vitro assay data on pages 57-65. There are no working examples present for the treatment of any disorder. There are no test(s) directed to the many uses pointed out above which are art-recognized for predicting in vivo efficacy.

The uses covered by the claims is not enabled based solely on the assay testing reported in the specification. Various studies reported for compounds in clinical development rely on animal models and not simply assay testing as done herein. Note Hoffman V. Klaus 9 USPQ2d 1657 regarding the standard of testing that is necessary to establish the likelihood of in vivo use. Also see Ex parte Powers 220 USPQ 925. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte Jovanovics 211 USPQ 907. Any evidence relied on by applicants must clearly show a

reasonable expectation of in vivo success for any additional diseases that may still be embraced in response to this action. See MPEP 2164.05(a).

Further, there is no disclosure regarding how all types of the diseases having diverse mechanisms are treated. Receptor activity is generally unpredictable and a highly structure specific area, and the data provided is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The breadth of the claims

The breadth of the claims are a method of inhibiting the reuptake of norepinephrine, which, as stated in the specification, is useful for the treatment of diseases such as pain, Alzheimer's disease, urinary incontinence and ADHS and for the treatment of diseases associated with norepinephrine dysfunction, including both curative and prophylactic treatment.

Furthermore, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided.

Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of all diseases would be benefited (treated) by inhibition of the reuptake of norepinephrine and would furthermore then have to determine which of the claimed compounds would provide treatment of which disease, if any.

The level of the skill in the art

While the level of skill in the art is high, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity. Furthermore, the claims cover (but are not limited to) all types diseases associated with the reuptake of norepinephrine. The state of the art is that drugs having the activity relied on herein are not known to have such a spectrum of clinical applications.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the instant claims for the treatment of disorders associated the reuptake of norepinephrine. As a result necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of the instant claims in order to

practice the claimed invention.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instantly claimed methods. In view of the breadth of the claim, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compounds in regards to the treatment or prevention of the many differing diseases, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 8, 9, 14, 15 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over GB 1,412,546.

Determining the scope and contents of the prior art

GB 1,412,546 discloses the compound of the formula (I) on page 1 which is useful for the treatment of depression, page 2. Pharmacuetical compositions are found on page 2. Processes of preparation are found on page 1, such as process (a) wherein R2 can be alkoxycarbonyl or aryloxy carbonyl and process (b) wherein Z can be halogen. Specific compounds disclosed are, example 1, page 3, 2-(2-n-propoxyphenylthio)-methylmorpholine hydrochloride; 2-)2-ethoxyphenyl-

thio)methylmorpholine hydrochloride; example 3, 2-(2-methylphenylthio)methylmorpholine hydrogen oxalate; example 4, 2-(2-n-butoxyphenyl)-thio)methylmorpholine, etc.

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the claims at issue is that the prior art has a hydrogen at the position equivalent to applicants' X which can be a C1-4 alkyl.

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to one of ordinary skill in the art to prepare applicants' instantly claimed compound, utilize applicants' instantly claimed process of preparation or apply applicants methods of treatment when faced with the prior art of record which disclosed compounds which differ only by having a hydrogen in the position equivalent to applicants' X which can be a C1-4alkyl group. it is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. In re Wood, 199 U.S.P.Q. 137 (C.C.P.A. 1978) and In re Lohr, 137 U.S.P.Q. 548, 549 (C.C.P.A. 1963). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (ie., an anti-depressant). Additionally, to those skilled in chemical art, one homologue is not such an advance over adjacent member of series as requires invention because chemists knowing properties of one member of series would in general know what to expect in adjacent members. In re Henze, 85 USPQ 261 (1950). The instant claimed compounds would have been obvious because one skilled in the art would have been

motivated to prepare homologs of the compounds taught in the reference with the expectation of obtaining compounds which could be used in the treatment of depression. Therefore, the instant claimed compounds would have been suggested to one skilled in the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday from 6:00am until 2:30pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*/Rebecca Anderson/
Primary Examiner, AU 1626*

22 August 2007

Rebecca Anderson
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